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Active seizures are associated with reduced adaptive functioning in children with epilepsy

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Children with epilepsy are at risk of suboptimal adaptive functioning. Research has not yet established how specific seizure and treatment variables may affect adaptive functioning, which would allow clinicians to better identify at-risk children. This study sought to determine the seizure and treatment variables predictive of adaptive functioning. Forty-six children with epilepsy participated in this study. Using multiple regression, active seizures (one or more seizures in the prior year) significantly predicted scores on the General Adaptive Composite of the Adaptive Behavior Assessment System-II. The active seizures variable uniquely explained 19% of the variance in adaptive functioning, with children with active seizures demonstrating significantly poorer adaptive functioning. The number of current AEDs, past AEDs, seizure types, age at seizure onset, and temporal lobectomy were not significant predictors. Post hoc analyses that divided the active seizures group according to seizure frequency in the prior month did not find significant differences in adaptive functioning. The results of this study suggest that children with seizures that are not fully controlled are at greater risk of suboptimal adaptive functioning.

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One percent of the population under 20 years of age will develop epilepsy, which is one of the most common neurological conditions in children.[1] The adverse effects of epilepsy and its treatments have been assessed on many different aspects of children's functioning; however, their impact on adaptive functioning has not been widely researched. Adaptive functioning refers to people's ability to take care of themselves and interact with and assist others at an age-appropriate level. Impairments in adaptive skills can significantly impact daily life as these skills are necessary to live, work, and play in the community.[2] Children with epilepsy, particularly those with medically intractable epilepsy, are likely to require increased supervision from adults which may interfere with the development of independence and with social functioning. Furthermore, the social stigma associated with epilepsy[3] may limit social opportunities and thereby hamper social development. Research is needed to establish how epilepsy, treatments (e.g. anti-epileptic drugs), and neurosurgery may impact the development of skills necessary for age-appropriate adaptive functioning either positively, for example, by reducing seizure frequency or negatively, for example, through side effects such as fatigue.

Research using adaptive functioning as an outcome variable is limited in children with epilepsy. Not surprisingly, children with intractable epilepsy, younger age at epilepsy onset, and those with a longer duration of epilepsy prior to surgical resection have been shown to be at risk of deficits in adaptive functioning.[4–6] Of note, however, a study by Chapieski et al.[7] showed that even children whose seizures were well-controlled on a single anti-epileptic drug (AED) were at risk of failure to make developmentally appropriate gains in adaptive skills over time. This suggests that the relationship between adaptive functioning and epilepsy may be a complex one that is not fully explained by markers of epilepsy severity. What we do know is that a diagnosis of epilepsy places children at risk of adaptive problems, and that more research addressing adaptive functioning and its correlates is needed.

This study sought to identify the seizure and treatment variables most strongly associated with adaptive functioning in order to aid clinicians in identifying children at greatest risk of suboptimal outcome. Building from research examining the relationship between specific seizure variables and cognitive outcome,[8–11] we hypothesized that younger age at seizure onset, active seizures, higher number of current AEDs, higher number of past AEDs, and multiple seizure types would be negatively associated with independent living skills. We also hypothesized that undergoing a temporal lobectomy would be positively related to adaptive functioning.[10]

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1. Methods

1.1. Participants

All participants were referred to a neuropsychology department affiliated with a comprehensive epilepsy center at a metropolitan children's hospital in the southeast. The Institutional Research Board approved this study and informed consent/assent was obtained from all families. Inclusion was contingent on a diagnosis of epilepsy made by a pediatric Epileptologist, with EEG support. Children who were diagnosed with a brain tumor were eligible for participation if they had not been treated with radiation or chemotherapy. Participants diagnosed with attention deficit/hyperactivity disorder (AD/HD; $n = 12$) or with a history of traumatic brain injury ($n = 1$) were eligible to participate given their typically high rates of comorbidity with epilepsy. Children with Chiari Type 1 Malformations ($n = 3$) were eligible to participate because this structural defect is not reliably associated with neurocognitive impairments, but rather is typically associated with physical symptoms such as dizziness, headache, neck pain, and muscle weakness.[12] Children with epilepsy who were diagnosed with a co-morbid neurological condition (e.g., autism, cerebral palsy) or progressive epilepsy syndrome were excluded. One hundred and sixteen families were eligible to participate. Families who participated in this study and those who did not were not appreciably different with respect to demographic variables. Twenty-three families were unable to be located, 3 families declined participation, and 31 families did not answer phone calls about participation. Fifty-eight families consented to participate, and 46 completed participation. See Table 1 for demographic and seizure data.

Twenty-six children had active seizures, defined as one or more seizures in the last year, while 20 children had controlled seizures.[13] Within the active seizures group, the mean seizure frequency over the last month was 17.81 ($SD = 34.05$; $Range = 0$–150; $Mode$ ($n = 10$) = 0) seizures. Sixteen children had seizures emanating from only the temporal lobe (active seizures = 7, controlled seizures = 9), while 30 children had extratemporal seizures (active seizures = 19, controlled seizures = 11). MRI scans were within normal limits for 27 children (active seizures = 17, controlled seizures = 10). Of the 19 children with abnormalities on MRI, 6 were in the right temporal region (active seizures = 1, controlled seizures = 5), 6 in the left temporal region (active seizures = 4, controlled seizures = 2), and 7 were extratemporal (active seizures = 4, controlled seizures = 3). For children who underwent a focal temporal lobe resection ($n = 14$), adaptive functioning was assessed at least 1 year post-surgery ($M = 2.42$ years ago, $SD = 1.56$, range = 1.00–5.00 years since surgery) to allow sufficient time for recovery. Eight of these children had controlled seizures (5 of whom had resections of brain tumors), and 6 had active seizures (3 of whom had brain tumors). Among children who had surgery, all underwent unilateral surgical resection of the temporal lobe (9 right, 3 (33%) of whom had active seizures, 5 left, 3 (60%) of whom had active seizures), and all surgeries were performed by the same neurosurgeon.

Of the 9 children diagnosed with AD/HD, 6 had active seizures and 3 had controlled seizures. Five children were born prematurely (active seizures = 3, controlled seizures = 2). Six children were delayed in reaching motor milestones (active seizures = 5, controlled seizures = 1), and 8 in reaching language milestones (active seizures = 7, controlled seizures = 1). All children had undergone a prior assessment of intellectual functioning. For the active seizures group, IQ was assessed when children were on average 11.49 ($SD = 3.31$) years old, with the mean falling in the low average range ($M = 88.38$, $SD = 18.28$), and 6 children with scores in the mentally retarded range. For the controlled seizures group, IQ was assessed when children were on average 11.78 ($SD = 3.02$) years old, with the mean falling in the average range ($M = 94.10$, $SD = 16.78$), and 2 children with scores in the mentally retarded range.

Table 1
Patient and seizure characteristics according to whether seizures are active ($n = 26$) or controlled ($n = 20$).

	Active seizures	Controlled seizures
Mean age at seizure onset	5.52 (3.66)	6.55 (4.89)
Mean time since seizure onset	7.74 (4.60)	7.59 (4.18)
Mean age at ABAS-II	13.29 (3.32)	14.18 (3.12)
Male:female	19:7	12:8
Caucasian:African American	22:4	17:3
Right:left-handedness	17:9	19:1
Socioeconomic Status	1.88 (.86)	1.95 (1.00)
Mean years of maternal education	15.15 (2.54)	14.20 (2.28)
Mean years of paternal education	14.76 (2.47)	14.11 (2.62)
Number with IEP at school	17	6
Mean ABAS-II GAC	81.65 (16.69)	100.05 (20.01)
Mean IQ	88.38 (18.28)	94.10 (16.78)
Current AEDs		
None	1	3
One	10	14
Two	13	3
Three	2	0
Number of past AEDs		
None	3	5
One	6	7
Two	3	4
Three	5	2
Four	1	0
Five or more	8	2
Number with focal seizures	5	4
Number with generalized seizures	7	8
Number with both focal and generalized seizures	14	8
Mean number of seizure types	2.19 (1.13)	1.90 (1.02)
Absence	14	10
Atypical absence	1	2
Tonic-clonic	15	10
Complex partial	14	11
Simple partial	7	2
Spasms	1	2
Myoclonic	2	0
Eyelid myoclonia	1	0
Gelastic	1	0
Febrile[a]	1	2
Status epilepticus	2	1
Number who underwent a TLE	6 (3 right, 3 left)	8 (6 right, 2 left)
Number with a brain tumor	3	5
Number with a Chiari Malformation	2	1
Number with AD/HD	9	3
Number with TBI	1	0

Note: Active seizures were defined as one or more seizures in the last year. Socioeconomic status was scored on a 5-point scale[19] with 1 representing the highest socioeconomic status and 5 the lowest.
Abbreviations: ABAS-II, Adaptive Behavior Assessment System-II; GAC, General Adaptive Composite; IQ, intellectual quotient; AED, anti-epileptic drug; TLE, temporal lobectomy.
[a] All patients with febrile seizures had at least one unprovoked seizure type.

1.2. Measures

Adaptive functioning: The Adaptive Behavior Assessment System-II (ABAS-II)[14] was designed to assess whether an individual displays the functional skills necessary for age-appropriate daily living without the assistance of others. A parent completed this paper and pencil questionnaire. The General Adaptive Composite (GAC) was used, and is comprised of 3 domains: Conceptual, Social, and Practical.

Table 2
Correlation matrix between seizure and treatment variables and adaptive functioning of ABAS-II GAC.

	GAC	Age at seizure onset	Active seizures	Number of current AEDs	Number of past AEDs	Number of seizure types
Age at seizure onset	.20	–				
Active seizures	−.46*	−.12	–			
Number of current AEDs	−.25	−.30*	.44**	−.03		
Number of past AEDs	−.15	−.25	.26	.43**	–	
Number of seizure types	−.12	−.03	.14	−.03	.14	−.03
Temporal lobectomy	−.02	.41**	−.18	−.33*	−.12	−.13

* $p < .05$
** $p < .01$.

Seizure variables: Age at seizure onset was measured in years. Active seizures was a dichotomous variable with 0 defined as no seizures in the past 12 months (controlled) and 1 defined as 1 or more seizures in the past 12 months (active).[13] This variable was chosen because of concerns about the accuracy of parent report of seizure counts.[15] Akman et al. found that parents under-reported seizure frequency, with only 38% of seizures accurately reported. Seizures in young children and children with absence seizures were particularly prone to being missed.[15] Number of current AEDs was a continuous variable reflecting the current number of medications a child was taking for seizure control at the time the ABAS-II was completed. Past AEDs was a continuous variable indicating the total number of medications a child has been prescribed in the past for seizure control. Multiple seizure types was continuous variable reflecting the number of different seizure types a participant had experienced. Temporal lobectomy was a dichotomous variable with 0 representing no surgical intervention and 1 representing that a temporal lobectomy was conducted.

Intelligence: Intellectual functioning was assessed using either the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; $n = 24$)[16] or Wechsler Abbreviated Scale of Intelligence (WASI; $n = 22$)[17]. Intellectual functioning was not assessed concurrently with the ABAS-II, but rather between 1 and 5 years previously ($M = 2.03$ years, $SD = 1.13$).

1.3. Experimental design and analyses

Families who consented to participate completed the ABAS-II and a seizure information form on their child. *t*-Tests, Chi-Square, and Fisher's Exact Tests were used to test for significant differences in demographic, seizure, and treatment variables between children with active and controlled seizures. Age at seizure onset and time elapsed since first seizure were found to be highly correlated ($r = -.72$, $p < .001$), so the latter was dropped from the model. Correlations between study variables are presented in Table 2. Multiple regression was used with seizure and treatment variables as the predictor variables and the GAC of the ABAS-II as the criterion variable. As there was not sufficient evidence to justify entering the predictor variables hierarchically, they were entered into the regression in a single step. Hypothesis tests were two-tailed.

2. Results

Prior to testing our hypotheses, the demographic and seizure variables presented in Table 1 were examined for significant between group differences. The mean number of current AEDs was significantly higher for the active seizures group ($t(44) = -3.31$, $p = .002$). Children with active seizures were significantly more likely to have an Individualized Education Plan (IEP) in place (χ^2 (1, $n = 46$) = 5.66, $p = .02$). The active seizures group also had significantly more children who were left-handed (*Fisher's Exact* (1, $n = 46$) = 5.83, $p = .03$). Scores on the GAC were significantly lower for children with active seizures ($t(44) = 3.40$, $p = .001$). An earlier estimate of IQ did not show significant differences between the groups ($t(44) = 1.09$, $p = .28$). No other seizure or demographic variables were significantly different between groups.

Mean adaptive functioning was at the lower end of the average to the higher end of the low average range regardless of current treatment status: prescribed one AED ($n = 17$; $M = 90.24$, $SD = 22.43$), prescribed multiple AEDs ($n = 15$; $M = 89.47$, $SD = 14.62$), and post-temporal lobectomy ($n = 14$; $M = 89.14$, $SD = 23.76$). Eight children with active seizures (31%) had scores on the GAC in the impaired range, while 2 children in the controlled seizures group had scores in the impaired range (10%). Results of the regression are presented in Table 3. The active seizures variable significantly predicted scores on the GAC, with children with active seizures performing more poorly on the GAC. Age at seizure onset, number of current AEDs, number of past AEDs, number of seizure types, and whether a temporal lobectomy was performed were not significantly predictive of adaptive functioning. Overall, our model accounted for 27% of the variance on the GAC, with the active seizures variable uniquely explaining 19% of the variance.

2.1. Post hoc analyses

The active seizures variable strongly predicted scores on the GAC. This variable was used in lieu of a count of seizure frequency owing to growing concerns about the accuracy of parent counts. However, over the month prior to study participation, parent report of seizure frequency in the active seizures group ranged from no seizures to as many as 150 seizures, suggesting highly variable levels of seizure control. In order to examine the appropriateness of using the dichotomous grouping of active or controlled seizures, we subdivided the active seizures group into children who had less than 4 seizures a month ($n = 14$) and those who had more frequent seizures ($n = 12$). *t*-Tests showed that IQ scores ($t(24) = 1.08$, $p = .29$) and scores on the GAC were not significantly different ($t(24) = 1.06$, $p = .30$), indicating that children in these subdivisions of the active seizures group were not functioning at a significantly different level on these measures.

3. Discussion

The findings of this study suggest that children who have had one or more seizures in the past year may be at greater risk of

Table 3
Standardized beta coefficients showing the ability of seizure variables to predict adaptive functioning (ABAS-II GAC).

	Adaptive functioning
Age at seizure onset	.22
Active seizures	−.43**
Number of current AEDs	−.10
Number of past AEDs	.05
Number of seizure types	−.10
Temporal lobectomy	−.23

** $p < .01$.

suboptimal adaptive functioning according to parent report. Inconsistent with our hypotheses, no other seizure or treatment variables were significantly associated with adaptive functioning. Seizure and treatment variables have been found to be predictive of other outcome variables in different studies, and the lack of findings here may be due to the small sample size or the heterogeneity of this sample, which did not exclusively examine children with a specific site of seizure focus (e.g., left temporal), with a specific type of seizure (e.g., complex partial), or children who belonged to a specific subgroup (e.g., children with new-onset epilepsy). Although additional studies are needed, the lack of predictive utility for the remaining seizure and treatment variables raises the possibility that they may contribute little additional variance to understanding adaptive functioning in a heterogeneous epilepsy sample.

Results indicated that children with active seizures were functioning at a significantly lower adaptive level not only compared to normative data, but also compared to participants in this study with controlled seizures. In the controlled seizure group, mean adaptive functioning was in the average range. In the active seizure group, mean adaptive functioning was in the low average range. This difference between children with active and controlled seizures was particularly striking given the similar mean age at epilepsy onset and mean length of epilepsy duration between groups. Although IQ was not assessed concurrently with the ABAS-II, an earlier mean estimate failed to show significant differences between children with active and controlled seizures, suggesting that adaptive functioning may be particularly sensitive to continuing seizures.

Reduced adaptive functioning in children with active seizures may be associated with a combination of both environmental and neurological factors. With respect to environmental factors, it is possible that parents place greater restrictions on their child's independence while they continue to have seizures to ensure their child's safety and well-being. Additionally, children who continue to have seizures may be more socially isolated as a result of stigmatization,[3] which could reduce their opportunities to develop age-appropriate independent living skills. With respect to neurological factors, the brain's continued abnormal functioning as evidenced by persistent seizures and the potential for continued inter-ictal disturbance may interfere with the development of children's adaptive skills and/or their ability to evidence adaptive behavior in age-appropriate circumstances. Furthermore, the active seizures variable was positively correlated with the number of AEDs a child was taking ($r = .44$, $p < .01$), suggesting a potentially confounding effect of AEDs and their side effects or possibly the medically refractory nature of some seizures to multiple medications. Although the results of this study do not allow for a clear determination of the degree of influence of these potential environmental and neurological factors, children with active seizures were significantly more likely to have an IEP in place at school than children with controlled seizures (65% versus 17%). No significant differences in socioeconomic status or years of parent education were evident, suggesting that the greater prevalence of IEPs may be an indirect marker of more pervasive neurological dysfunction or disruption in children with active seizures. This should, however, be interpreted cautiously as children in the active seizures group were not significantly more likely to have a structural abnormality on MRI, have been born prematurely, or have been delayed in reaching developmental milestones.

The predictive utility of the active seizure variable warrants attention, particularly as researchers are challenging the accuracy of self-report of seizure frequency in adults [e.g.,[18]] and parent report of seizure frequency in children.[15] The latter study found that parents, on average, missed 62% of seizures, which raises grave concern about the validity of seizure counts. Additionally, many parents told us that they had difficulty calculating seizure frequency (particularly when their child experienced absence or nocturnal seizures). Breaking down the active seizures variable based on whether children had more or less than/equal to 4 seizures in the prior month did not result in significant differences in adaptive functioning or prior intellectual functioning. This may be due to measurement error or to the use of an arbitrary cut-off, but it also may indicate that complete seizure control is important for the development and maintenance of adaptive skills. The results of this study suggest that categorizing seizures as active or controlled may be a meaningful estimate of current seizure burden that is easier for parents to report than frequency, and which may be subject to less measurement error and increased reliability.

This study was limited by the size of our sample, which prevented us from having sufficient power to examine the influence of other variables of interest. Furthermore, the heterogeneity of the sample prevented the examination of the impact of specific AEDs or combinations of AEDs, seizure types, and co-morbid diagnoses on adaptive functioning. Less than half of eligible families participated in this study, which, while largely due to difficulties reaching families, may also have biased the data, perhaps in favor of children with more severe epilepsy. Thus, it will be important to confirm these findings in a sample with a higher response rate. Additionally, the study would have benefited from a concurrent neuropsychological assessment to allow for the examination of adaptive functioning within the broader context of a child's overall neuropsychological functioning. However, several potential confounds including the frequency of neurosurgery and brain tumors, socioeconomic status, age at epilepsy onset, and an earlier estimate of intellectual functioning were not significantly different between the active seizures and control groups. In the context of the above limitations, this study is able to highlight the detrimental association between seizures within the past year and month and adaptive functioning.

In light of the limited research on adaptive functioning in children with epilepsy, there are numerous directions for potential research. These include confirming the utility of the active seizures variable in explaining adaptive functioning, and testing whether this variable also may be of use in explaining variance in other areas of neuropsychological functioning. A better understanding of the underlying reason for the strong predictive utility of the active seizures variable is warranted. Future research also is needed to determine the clinical utility of categorizing seizures as active and controlled. More studies on the influence of active seizures on adaptive functioning that include longitudinal assessment of adaptive functioning will help to clarify how adaptive functioning abilities change as seizure and treatment variables are modified as well as teasing apart the influence of continued seizures from the effects of a priori neurological insults on adaptive functioning. Additionally, possible differential AED effects on adaptive functioning should be examined.

The findings of this study suggest that children with epilepsy are at risk of significant adaptive impairments. Having one or more seizures in the last year was associated with a significantly higher risk of suboptimal adaptive functioning compared to children with controlled seizures. Further subdividing the active seizures group based on seizure frequency was not associated with differences in adaptive abilities, suggesting that all children who continue to have seizures, even if their seizures are considered well-controlled, are at risk of adaptive deficits.

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